

WHAT IS CLAIMED IS:

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1. A method for altering the cell fate otherwise adopted by a cell comprising:
  - (a) altering Notch pathway function in the cell by a method comprising contacting the cell *in vitro* with, or administering to an organism comprising the cell, an agonist or antagonist of Notch pathway function in the cell;
  - (b) concurrently with step (a), altering the function of a cell fate control gene pathway in the cell by a method comprising contacting the cell *in vitro* with, or administering to an organism comprising the cell, an agonist or antagonist of a cell fate control gene pathway function in the cell, wherein the cell fate control gene pathway is not the Notch pathway; and
  - (c) subjecting the cell to conditions that allow cell fate determination to occur.
2. The method according to claim 1 comprising contacting the cell *in vitro* with an agonist of Notch pathway function.
3. The method according to claim 2 which further comprises contacting the cell *in vitro* with an agonist of a cell fate control gene pathway function.
4. The method according to claim 2 which further comprises contacting the cell *in vitro* with an antagonist of a cell fate control gene pathway function.
5. The method according to claim 1 comprising administering to an organism comprising the cell an agonist of Notch pathway function and an agonist of a cell fate control gene pathway function.
6. The method according to claim 1 comprising administering to an organism comprising the cell an agonist of Notch pathway function and an antagonist of a cell fate control gene pathway function.
7. The method according to claim 1 comprising introducing into the cell one or more nucleic acids encoding an agonist of Notch pathway function and an agonist of a cell fate control gene pathway function such that the agonists are

expressed by the cell.

8. The method according to claim 1 comprising introducing into the cell one or more nucleic acids encoding an agonist of Notch pathway function and an antagonist of a cell fate control gene pathway function such that the agonist and antagonist are expressed by the cell.

9. The method according to claim 1 wherein the agonist of Notch pathway function is a dominant-active Notch mutant.

10. The method according to claim 1 wherein the agonist is purified.

11. The method according to claim 5 which comprises administering to the organism one or more cells recombinantly expressing the agonist of Notch pathway function and the agonist of the cell fate control gene pathway function.

12. The method according to claim 6 which comprises administering to the organism one or more cells recombinantly expressing the agonist of Notch pathway function and the antagonist of the cell fate control gene pathway function.

13. The method according to claim 1 comprising contacting the cell *in vitro* with an antagonist of Notch pathway function.

14. The method according to claim 13 which further comprises contacting the cell *in vitro* with an agonist of a cell fate control gene pathway function.

15. The method according to claim 13 which further comprises contacting the cell *in vitro* with an antagonist of a cell fate control gene pathway function.

16. The method according to claim 1 comprising administering to an organism comprising the cell an antagonist of Notch pathway function and an agonist of a cell fate control gene pathway function.

17. The method according to claim 1 comprising administering to an organism comprising the cell an antagonist of Notch pathway function and an

antagonist of a cell fate control gene pathway function.

18. The method according to claim 1 comprising introducing into the cell one or more nucleic acids encoding an antagonist of Notch pathway function and an agonist of a cell fate control gene pathway function such that the antagonist and agonist are expressed by the cell.
19. The method according to claim 1 comprising introducing into the cell one or more nucleic acids encoding an antagonist of Notch pathway function and an antagonist of a cell fate control gene pathway function such that the antagonists are expressed by the cell.
20. The method according to claim 1 wherein the antagonist of Notch pathway function is a dominant-negative Notch mutant.
21. The method according to claim 1 wherein the antagonist is purified.
22. The method according to claim 16 which comprises administering to the organism one or more cells recombinantly expressing the antagonist of Notch pathway function and the agonist of the cell fate control gene pathway function.
23. The method according to claim 17 which comprises administering to the organism one or more cells recombinantly expressing the antagonist of Notch pathway function and the antagonist of the cell fate control gene pathway function.
24. The method according to claim 1 in which the cell fate control gene encodes a transcription factor.
25. The method according to claim 23 in which the transcription factor is a homeodomain protein.
26. The method according to claim 25 in which the homeodomain protein is a Pax protein.
27. The method according to claim 26 in which the Pax protein is selected from

the group consisting of human or mouse Pax-1, Pax-2, Pax-3, Pax-4, Pax-5, Pax-6, Pax-7, Pax-8 or Pax-9 and *Drosophila* Eyeless and Twin of Eyeless.

28. The method according to claim 25 in which the homeodomain protein is a Hox protein.

29. The method according to claim 28 in which the Hox protein is selected from the group consisting of Mammalian Hox A1-7, Hox A9-11 or HoxA13; Hox B1-9; Hox C4-6 or Hox C8-13; Hox D1, Hox D3-4 or Hox D8-13; and *Drosophila* Lab, Pb, Dfd, Scr, Antp, Ubx, Abd-A and Abd-B.

30. The method according to claim 25 in which the homeodomain protein is selected from the group consisting of a DLX protein, LIM homeodomain protein, PBC protein, MEINOX protein, POU protein, PTX protein and NKX protein.

31. The method according to claim 24 in which the transcription factor is selected from the group consisting of a Vestigial protein, MADS domain protein, bHLH protein, SOX protein and T-box protein.

32. The method according to claim 1 in which the cell fate control gene encodes a signaling molecule.

33. The method according to claim 32 wherein the signaling molecule is selected from the group consisting of a Hedgehog protein, a WNT protein, and a TGF  $\beta$ /BMP protein.

34. The method according to claim 1 which further comprises expanding the cell by subjecting the cell to cell growth conditions to produce a population of cells.

35. A method of treating a patient by provision of a cell transplant comprising producing cells of a particular cell fate according to the method of claim 34, and administering the cells to the patient.

36. A method of treating macular degeneration in a patient comprising agonizing Notch pathway function in retinal pigment epithelium or retinal

neuroepithelium of the patient.

37. The method according to claim 36 further comprising agonizing Pax6 pathway function.
38. The method according to claim 36 or 37, wherein agonizing Notch pathway function comprises contacting the retinal pigment epithelium or retinal neuroepithelium with a protein agonist of Notch pathway function.
39. The method according to claim 38 in which the protein agonist of Notch pathway function is selected from the group consisting of Delta and Serrate.
40. The method according to claim 36 or 37, wherein agonizing Notch pathway function comprises contacting the retinal pigment epithelium or retinal neuroepithelium with a nucleic acid encoding an agonist of Notch pathway function.
41. The method according to claim 40 in which the nucleic acid encodes a dominant active mutant of Notch, Delta or Serrate.
42. The method according to claim 37 wherein the patient is a human.
43. The method according to claim 42, wherein agonizing Pax6 pathway function comprises contacting the retinal pigment epithelium or retinal neuroepithelium with a nucleic acid encoding human Pax6.
44. The method according to claim 42, wherein agonizing Pax6 pathway function comprises contacting the retinal pigment epithelium or retinal neuroepithelium with recombinant human Pax6 protein functionally coupled to a nuclear internalization signal.
45. A method for changing the cell fate of a mature cell type comprising:
  - (a) antagonizing Notch pathway function in the cell by a method comprising contacting the cell *in vitro* with, or administering to an organism comprising the cell, an antagonist of Notch pathway function in the cell;
  - (b) after step (a) agonizing Notch pathway function in the cell by a

method comprising contacting the cell *in vitro* with, or administering to the organism comprising the cell, an agonist of Notch pathway function in the cell;

(c) concurrently with step (b), altering the function of a cell fate control gene pathway in the cell by a method comprising contacting the cell *in vitro* with or administering to the organism comprising the cell, an agonist or antagonist of cell fate control gene pathway function in the cell; and

(c) subjecting the cell to conditions that allow cell fate determination to occur.

46. A kit comprising in one or more containers (a) a molecule that alters Notch pathway function; and (b) a molecule that alters a cell fate control gene pathway.

47. The kit of claim 46 wherein the molecule of (a) is an agonist.

48. The kit of claim 46 wherein the molecule of (a) and the molecule of (b) are purified.

49. The kit of claim 47 wherein the molecule of (a) is a dominant-active Notch mutant or a nucleic acid comprising a sequence encoding such a mutant, said sequence operably linked to a promoter.

50. The method according to claim 1, 5, 6, 16 or 17 wherein the altering of cell fate is a change in tissue or organ type.

51. The method according to claim 1 wherein the cell is a mammalian cell.

52. The method according to claim 51 wherein the cell is a human cell.

53. A method for altering the cell fate otherwise adopted by a cell comprising:  
(a) altering Notch pathway function in the cell by a method comprising contacting the cell *in vitro* with or administering to an organism comprising the cell an agonist or antagonist of Notch pathway function in the cell; and

(b) subjecting the cell to conditions that allow cell fate determination to

occur while maintaining the alteration to Notch pathway function, until a cell of an altered cell fate is produced.

- 5 54. A method for producing an organ of a different type than would be otherwise produced by one or more cells by comprising:
- 10 (a) altering Notch pathway function in one or more cells by a method comprising contacting the cells *in vitro* with or administering to an organism comprising the cells an agonist or antagonist of Notch pathway function in the organ; and
- (b) subjecting the cells to conditions that allow organ differentiation and cell growth to occur while maintaining the alteration to Notch pathway function, until a population of cells forming an organ is produced.
- 15 55. The method according to claim 53 or 54 comprising contacting the cell *in vitro* with an agonist of Notch pathway function.
- 20 56. The method according to claim 53 or 54 comprising contacting the cell *in vitro* with an antagonist of Notch pathway function.
- 25 57. The method according to claim 53 or 54 which further comprises expanding the cell by subjecting the cell to cell growth conditions to produce a population of cells.
- 30 58. A method of treating a patient by provision of a cell transplant comprising producing cells of a particular cell fate according to the method of claim 53, and administering the cells to the patient.
- 35 59. A method of treating a patient by provision of an organ transplant comprising producing an organ of a particular type according to the method of claim 54, and administering the organ to the patient.
60. The method according to claim 53 or 54 wherein the cell is a mammalian cell.
61. The method according to claim 60 wherein the cell is a human cell.

5 62. The method according to claim 54 which further comprises concurrently with step (a) altering the function of a cell fate control gene pathway in the cell by a method comprising contacting the cell *in vitro* with, or administering to an organism comprising the cell, an agonist or antagonist of a cell fate control gene pathway function in the cell, wherein the cell fate control gene pathway is not the Notch pathway.

10 *Sub 4* 63. The method according to claim 1 wherein the agonist or antagonist of Notch pathway function, and the agonist or antagonist of a cell fate control gene pathway function, are purified.

15 *Sub B2* 64. The method according to claim 1 or 53, wherein the cell fate produced by said method is apoptosis.

65. The method according to claim 63 wherein the cell is a human cell.

66. The method according to claim 64 wherein the cell is a cancer cell.

20 67. A method for screening for agonists or antagonists of Notch pathway function, comprising:

- 25 (a) altering a cell fate control gene pathway function in a cell;  
(b) contacting the cell with or recombinantly expressing within the cell one or more test agonists or antagonists of Notch pathway function while subjecting the cell to conditions that allow cell fate determination to occur; and  
(c) examining the cell for an alteration in cell fate as compared to cells not contacted with or expressing the test agonists or antagonists.

30 68. A method for screening for agonists or antagonists of a cell fate control gene pathway function, comprising:

- 35 (a) altering Notch pathway function in a cell;  
(b) contacting the cell with or recombinantly expressing within the cell one or more test agonists or antagonists of cell fate control gene pathway function while subjecting the cell to conditions that allow cell fate determination to occur; and  
(c) examining the cell for an alteration in cell fate as compared to cells



not contacted with or ~~expressing~~ the test agonists or antagonists.

69. The method according to ~~claim 1 or 53~~, wherein the cell fate that would have been otherwise adopted by said cell is apoptosis.

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